UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/726,211	10/04/1996	MAR TORMO	UTXC:504	8827

7590 12/12/2003

DAVID L. PARKER
FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVENUE , SUITE 2400
AUSTIN, TX 78701

EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	45

DATE MAILED: 12/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/726,211	TORMO ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-30,44,46 and 57-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-30,44,46 and 57-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *22,41,44*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Non-Final Office Action is a response to the Request for Continued Prosecution Application filed 8 August 2002 and the "Substitute Preliminary Amendment and Remarks" filed 2 December 2002 (Paper No. 43). Claims 10 and 21 were amended and claims 57-93 were added in Paper No. 43. Claims 10-30, 44, 46 and 57-93 are pending and under consideration.

Claim Objections

Claim 66 is objected to because of the following informalities: The word "phospholipid" is misspelled in line 1. Appropriate correction is required.

Double Patenting

It is noted that copending application 09/381,747 appears to disclose subject matter in common with this application and may recite the same or overlapping Inventions. Since 09/381,747 is not presently available for review, no determination has been made as to whether or not a double patenting rejection should be applied to the claims of the instant application. If, upon availability of the above application to the Examiner, it is determined that there are conflicting claims between 09/381,747 and the instant application, double patenting will not be considered as new ground(s) of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-20, 44, 88 and 91 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting proliferation of a disease cell having a t(14;18) translocation comprising administering a first polynucleotide that hybridizes to a second polynucleotide under intracellular conditions, wherein said first polynucleotide comprises at least 8 consecutive bases complementary to the translation initiation site the translation initiation site of Bcl-2 mRNA, does not reasonably provide enablement for the method wherein only the second polynucleotide is limited to comprising 8 bases of the translation initiation site of Bcl-2 mRNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims are directed to a method of inhibiting proliferation of a cell comprising a t(14;18) translocation comprising administering a first polynucleotide that hybridizes to a second polynucleotide wherein the second

polynucleotide comprises at least 8 bases of the translation initiation site of Bcl-2 mRNA. According to the claim, the only limitation of said first polynucleotide is that it hybridizes to said second polynucleotide. The second polynucleotide, which is the target for intervention, is limited only to comprising 8 bases of the translation initiation site of Bcl-2 mRNA. As these 8 bases are not limited to any specific order, the second polynucleotide need only comprise 8 of the nucleotides appearing in the translation initiation site of Bcl-2 mRNA in any order. As each of the four nucleotides found in naturally occurring nucleic acids appear at least twice in the translation initiation site of the Bcl-2 mRNA, the second nucleic acid logically encompasses all naturally occurring nucleic acids. Therefore, according to the broadest reasonable interpretation, the claims are directed to a method of inhibiting proliferation of a Bcl-2-associated disease cell comprising administering a first polynucleotide that hybridizes to any region of any nucleic acid.

State of the prior art and level of predictability in the art: Although the prior art teaches that antisense RNA and ribozymes can be used to suppress gene expression, these methods require detailed knowledge of the target molecule and empirical experimentation to identify an effective inhibitory molecule. In an article published well after the effective filing date of the instant application, Far et al. (*Bioinformatics* (2001) 17:1058-1061) teach that the "successful use of [antisense oligonucleotides] to suppress gene expression is somewhat limited since only a small portion of all possible antisense species against a given target sequence shows efficacy..." (page 1058, column 1, first paragraph of the introduction). Far also teaches that in spite of a considerable amount of empirical data on the use of antisense oligonucleotides, the work "does not seem to be reflected by the knowledge on the biophysical and biochemical level of the action of [antisense oligonucleotides] nor by the knowledge about the rules that govern the relationship

between specific sequences of [antisense oligonucleotides], the influence of the target structure, the annealing *in vitro*, and the efficacy *in vivo"* (beginning on page 1058, column 1, third from final line through the fourth line of column 2). Finally, Far teaches, "the effectiveness of [antisense oligonucleotides] is strongly dependent on local target RNA structures, on chemical properties and sequences of the [antisense oligonucleotide] species, and on the characteristics of the biological system of interest including the metabolic properties of the target RNA and the gene product, respectively" (page 1058, column 2, first full paragraph).

A recent article by Braasch *et al.* (*Biochem.* (2002) 41:4503-4510) emphasizes that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (page 4503, first and second paragraphs). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (page 4503, first and second paragraphs). Branch (1998) *Trends Biochem. Sci.* 23:45-50 (made of record in the IDS filed 29 July 1999) adds that "internal structures of target RNAs and their associations with cellular proteins create physical

barriers, which render most potential binding sites inaccessible to antisense molecules" (page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz *et al.* (1996) *Proc. Natl. Acad. Sci. USA* 93:3161-3163 (made of record in the IDS filed 29 July 2003) teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (page 3161, second and third columns).

Braasch *et al.* discuss the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism" (page 4503, paragraphs 1 and 2). Branch affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm *et al.* (2001) *Lancet* 358:489-497 states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Amount of direction provided by the inventor and existence of working examples: First, with regard to practicing the claimed method wherein the target nucleic acid is anything other than a Bcl-2 encoding mRNA, the specification is silent. There is no guidance to direct the skilled artisan in the identification of target nucleic acids other than Bcl-2 that would enable the

method of inhibiting proliferation of a Bcl-2-associated disease cell comprising a t(14;18) translocation.

With regard to practicing the claimed invention wherein the first polynucleotide does not hybridize to the translation initiation site of a Bcl-2 mRNA, the specification provides only general teachings of the structure of the Bcl-2 mRNA and descriptions of possible target regions (see especially the discussion at pages 10-14). However, the working examples are limited to a single oligonucleotide comprising 18 bases complementary to the translation initiation site of the human Bcl-2 mRNA. There is no evidence provided to indicate that inhibition of proliferation could be achieved with any oligonucleotide that does not comprise sequence complementary to the translation initiation site of the Bcl-2 mRNA.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the relevant art is high, the ordinary skilled artisan would not be able to make the full scope of the claimed method. The instant disclosure provides description of the process of making the invention in full, clear, concise and exact terms as to enable one skilled in the art to practice the method only insofar as the first oligonucleotide comprises sufficient sequence complementary to the translation initiation site of Bcl-2 to provide hybridization under intracellular conditions. Beyond this scope, the specification merely speculates that nucleic acids comprising sequence complementary to other portions of the Bcl-2 mRNA could be used in the method. However, given the art recognized unpredictability of obtaining effective antisense oligonucleotides, the skilled artisan could not practice the full scope of the claimed method without blindly making and testing each and every polynucleotide capable of hybridizing to the second polynucleotide of the claims. Clearly the amount of experimentation

involved would be undue. Thus, due to the art recognized unpredictability of obtaining effective antisense oligonucleotides and the lack of guidance in the specification or prior art with regard to how to make the required oligonucleotides, it would require undue experimentation to practice the invention commensurate with the full scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-30, 66-71, 77, 78, 90 and 93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28-30 are each indefinite in the recitation of "said composition". There is no antecedent basis for this limitation in the claims from which the rejected claims depend. Amending the claims to recite "said association" instead of "said composition" would obviate this rejection.

Claim 66 is indefinite in being directed to a composition comprising an antisense oligonucleotide complementary to the translation initiation site of Bcl-2 mRNA wherein the translation initiation site comprises SEQ ID NO: 1. The Bcl-2 mRNA disclosed in the application does not comprise SEQ ID NO: 1, which is, in fact, complementary to sequence found within the translation initiation site of the Bcl-2 mRNA. As there is no disclosure of a Bcl-2 mRNA comprising SEQ ID NO: 1, it is unclear what is being claimed. Amending the claim such that the antisense oligonucleotide of the composition comprises SEQ ID NO: 1 would

overcome this rejection. Claims 67-71, 77, 78 and 90 are indefinite insofar as they depend from claim 66.

Claim 91 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are those recited in claim 31, from which claim 91 depends. Claim 31 was canceled in a previous Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-18, 21-28 44, 46, 57-72, 74-76, 78-83 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reed (WO/ 9508350; previously made of record) in view of Tari *et al.* (1995) U.S. Patent No. 5,417,978.

Reed teaches a composition comprising an antisense polynucleotide comprising the sequence set forth in the instant application as SEQ ID NO: 1, which is complementary to the translation initiation site of Bcl-2 and capable of hybridizing to a Bcl-2-encoding polynucleotide under intracellular conditions (see especially "TI-AS" described in the first paragraph on page 4 and in the Table I on page 13). Reed further teaches that the composition may comprise liposomes (see especially the first full paragraph on page 14) and that the polynucleotide can be comprised within an expression construct. Thus, Reed teaches all of the limitations of the instant claims 57, 65, 66, 72 and 81 except for a neutral phospholipid. However, Reed does teach that that the polynucleotide may comprise methylphosphonate (see especially the paragraph bridging pages 8-9 and Examples 15-16).

Tari *et al.* teaches the delivery of antisense methylphosphonate oligonucleotides by encapsulation of said oligonucleotides in liposomes formed from the neutral phospholipid DOPC. In view of the teachings of Tari *et al.* it would have been obvious to one of ordinary skill in the art at the time the invention was made to select neutral phospholipids for the composition comprising methylphosphonate anti-Bcl-2 oligonucleotides and liposomes taught by Reed. Tari *et al.* teaches the benefit of using compositions consisting of neutral phospholipids and

methylphosphonate oligonucleotides, including improved stability of the antisense oligonucleotide compositions under biologic conditions, improved uptake of the composition in cells, improved incorporation efficiency of the oligonucleotides into liposomes, and enhance specific therapeutic effect of the antisense oligonucleotides against CML and other disease conditions (column 2, lines 49-56). Tari *et al.* also points out that the phospholipid PC is particularly well indicated for use with methylphosphonate oligonucleotides because both PC and MP are neutral molecules and because PC is a well-studied lipid and easily handled.

These teachings make clear that compositions comprising methylphosphonate nucleic acids, comprising sequence complementary to the translation initiation site of Bcl-2, and liposomes according to the instant claimed invention were known in the art at the time of filing (Reed), and that there was ample motivation to use the neutral phospholipid PC in making the liposomes of the composition because, as Tari *et al.* teaches, PC is compatible with methylphosphonate, a well-studied lipid and easy to handle.

Independent claims 10 and 21 each encompass a method of inhibiting proliferation of a Bcl-2 associated disease cell comprising making a composition comprising a polynucleotide that hybridizes to the translation initiation site of Bcl-2 and a neutral phospholipid. For reasons set forth above, the composition of the claims is obvious in view of the teachings of Reed and Tari *et al.* Furthermore, as Tari *et al.* teaches that the composition comprising an oligonucleotide and a neutral phospholipid comprises the steps of mixing the oligonucleotide with the neutral phospholipid (see especially the second full paragraph in column 5), the method of making the composition set forth in the claims would also be obvious to the skilled artisan.

The method of claims 10 and 21 further comprises administering the composition to a Bcl-2-associated disease cell comprising a t(14;18) translocation. Reed teaches that the methods of the invention disclosed therein are suitable for inhibiting growth of lymphoma/leukemia cells that express the human Bcl-2 gene and have a t(14;18) chromosomal translocation (first full paragraph on page 3). Reed *et al.* further contemplates administering the disclosed compositions to patients by any effective route (see especially the discussion beginning at the paragraph bridging pages 14-15 and continued through the second paragraph on page 17). Reed *et al.* also discloses many examples of inhibition of tumor cell proliferation *in vitro* comprising administering antisense oligonucleotides capable of hybridizing with the translation initiation site of Bcl-2 mRNA. Thus, it would have also been obvious to one of ordinary skill in the art at the time the invention was made, based on the teachings found in Reed and Tari *et al.*, to administer a composition comprising a polynucleotide that hybridizes to the translation initiation site of Bcl-2 to inhibit proliferation of a cell comprising a t(14;18) chromosomal translocation.

Absent evidence to the contrary, one would have a reasonable expectation of success in using the DOPC liposomes of Tari *et al.* in the composition of Reed because Tari *et al.* demonstrates that the DOPC compositions can be effectively used to deliver antisense oligonucleotides (see especially the Examples described beginning in the paragraph bridging columns 6-7).

For these reasons, the invention of claims 10, 21, 57, 65, 66, 72 and 81, as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Furthermore, the limitations of dependent claims 11-18, 22-28, 44, 46, 58-64, 67-71, 74-76, 78-80, 82, 83 and 85 are each found within the teachings of Reed and Tari *et al.*

Reed *et al.* teaches: the method comprises administering the composition to inhibit the growth of a lymphoma cell comprising a t(14;18) translocation (*Id.*), which one of ordinary skill in the art would understand to particularly encompass follicular lymphoma according to claims 11, 12, 22 and 23; the method comprises administering to a human (*Id.*) according to the limitations of claims 16, 17, 26 and 27; an oligonucleotide having a length of between 8 and 50 bases according to claims 13 and 58 (see especially page 5, lines 9-11); a polynucleotide comprising SEQ ID NO: 1 according to claims 59, 60 and 67 (*Id.*); a liposome encapsulated polynucleotide and wherein the liposome consists of DOPC according to claims 14, 15, 24, 25, 44, 46, 61-64, 68-71, 74-76, 78-80, 82 and 83 (*Id.*); and 8 consecutive nucleotides of the sequence set forth as SEQ ID NO: 1 according to claim 85 (*Id.*). Finally, with regard to claims 18 and 28, limited to administering the oligonucleotide in a volume of between 0.5 ml and 10 ml, one of ordinary skill in the art would understand that the limitation amounts to a recitation of an infinite range of concentrations (i.e., an unlimited quantity of active ingredient administered in a range of volumes). M.P.E.P. §2104.05(II) states, "[g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. '[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.' In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In the instant case the concentration could not possibly be critical because it is essentially unlimited. Thus, the limitations of each of claims 11-18, 20-28, 44, 46, 58-64, 67-71, 74-76, 78-80, 82, 83 and 85 would have been obvious to the ordinary skilled artisan at the time of filing.

Claims 10-18, 21-28 44, 46, 57-72, 73-85 and 91-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tormo *et al.* (1996) *Proc. Am. Assoc. Cancer Res. Ann. Meeting* 37:173 (previously made of record) in view of Tari *et al.* and in further view of Reed.

Tormo *et al.* teaches a composition comprising an antisense polynucleotide complementary to the first open reading frame of the Bcl-2 mRNA and liposomes. Thus, Tormo *et al.* teaches all of the limitations of the instant claims 57, 65, 66, 72 and 81 except for liposomes consisting of neutral phospholipids and that the antisense oligonucleotide should comprise a portion of SEQ ID NO: 1 or be complementary to the translational start site of Bcl-2. However, Tormo *et al.* teaches that the oligonucleotides are P-ethoxy analogs, which are non-ionic.

Tari *et al.* teaches the delivery of antisense non-ionic (i.e., methylphosphonate) oligonucleotides by encapsulation of said oligonucleotides in liposomes formed from the neutral phospholipid DOPC. In view of the teachings of Tari *et al.* it would have been obvious to one of ordinary skill in the art at the time the invention was made to select neutral phospholipids for the composition comprising p-ethoxy anti-Bcl-2 oligonucleotides and liposomes taught by Tormo *et al.* Tari *et al.* teaches the benefit of using compositions consisting of neutral phospholipids and non-ionic oligonucleotides, including improved stability of the antisense oligonucleotide compositions under biologic conditions, improved uptake of the composition in cells, improved incorporation efficiency of the oligonucleotides into liposomes, and enhance specific therapeutic effect of the antisense oligonucleotides against CML and other disease conditions (column 2, lines 49-56). Tari *et al.* also points out that the phospholipid PC is particularly well indicated for

use with non-ionic oligonucleotides because neutral molecules are compatible and because PC is a well-studied lipid and easily handled. As Applicant points out in Paper No. 43 (paragraph bridging pages 9-10), "The Tari patent stands merely for the proposition that it is desirable to combine a neutral phospholipid with a neutrally charged antisense so that they are 'compatible'."

Reed teaches a composition comprising the sequence set forth in the instant application as SEQ ID NO: 1, which is complementary to the translation initiation site of Bcl-2 and capable of hybridizing to a Bcl-2-encoding polynucleotide under intracellular conditions (see especially "TI-AS" described in the first paragraph on page 4 and in the Table I on page 13). Reed further teaches that the translation initiation site of Bcl-2 is a preferred strategic site and that an oligonucleotide comprising 5-20 bases of complementary to portions of the Bcl-2 gene coding strand flanking said initiation sequence are most preferable (first paragraph on page 4). These teachings provide both instruction and motivation to preferably use polynucleotides complementary to the translation initiation site of Bcl-2 to provide antisense inhibition of expression. Given these teachings, it would be obvious to one of ordinary skill in the art at the time the invention was made to use an oligonucleotide comprising all or a portion of the polynucleotide set forth in the instant application as SEQ ID NO: 1.

Thus, based on the teachings of Tormo *et al.*, Tari *et al.* and Reed, viewed as a whole, the composition of claims 57, 65, 66, 72 and 81 would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Independent claims 10 and 21 each encompass a method of inhibiting proliferation of a Bcl-2 associated disease cell comprising making a composition comprising a polynucleotide that hybridizes to the translation initiation site of Bcl-2 and a neutral phospholipid. For reasons set

forth above, the composition of the claims is obvious in view of the teachings of Tormo *et al.*, Tari *et al.* and Reed. Furthermore, as Tari *et al.* teaches that the composition comprising an oligonucleotide and a neutral phospholipid comprises the steps of mixing the oligonucleotide with the neutral phospholipid (see especially the second full paragraph in column 5), the method of making the composition set forth in the claims would also be obvious to the skilled artisan.

The method of claims 10 and 21 further comprises administering the composition to a Bcl-2-associated disease cell comprising a t(14;18) translocation. Both Tormo *et al.* and Reed teach that the methods of the invention disclosed therein are suitable for inhibiting growth of lymphoma/leukemia cells that express the human Bcl-2 gene and have a t(14;18) chromosomal translocation (first full paragraph on page 3 or Reed and the concluding sentence of Tormo *et al.*). Reed *et al.* further contemplates administering the disclosed compositions to patients by any effective route (see especially the discussion beginning at the paragraph bridging pages 14-15 and continued through the second paragraph on page 17). Tormo *et al.* and Reed *et al.* also discloses many examples of inhibition of tumor cell proliferation *in vitro* comprising administering antisense oligonucleotides capable of hybridizing with the translation initiation site of Bcl-2 mRNA. Thus, it would have also been obvious to one of ordinary skill in the art at the time the invention was made, based on the teachings found in Tormo *et al.* Reed and Tari *et al.*, to administer a composition comprising a polynucleotide that hybridizes to the translation initiation site of Bcl-2 to inhibit proliferation of a cell comprising a t(14;18) chromosomal translocation.

For these reasons, the invention of claims 10, 21, 57, 65, 66, 72 and 81, as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was

made. Furthermore, the limitations of dependent claims 11-18, 22-28, 44, 46, 58-64, 67-71, 73, 74-80, 82, 83-85 and 91-93 are each found within the teachings of Tormo *et al.*, Reed and Tari *et al.*

Tormo *et al.* teaches that the composition comprising a P-ethoxy oligonucleotide according to claims 73, 77, 84 and 91-93 and that the method can be used to inhibit the growth of a follicular lymphoma cell comprising a t(14;18) translocation (*Id.*) according to claims 11, 12, 22 and 23. Reed teaches the method comprising administering to a human (*Id.*) according to the limitations of claims 16, 17, 26 and 27; an oligonucleotide having a length of between 8 and 50 bases according to claims 13 and 58 (see especially page 5, lines 9-11); a polynucleotide comprising SEQ ID NO: 1 according to claims 59, 60 and 67 (*Id.*); a liposome encapsulated polynucleotide and 8 consecutive nucleotides of the sequence set forth as SEQ ID NO: 1 according to claim 85 (*Id.*). Finally, Tari *et al.* teaches the composition wherein the liposome consists of DOPC according to claims 14, 15, 24, 25, 44, 46, 61-64, 68-71, 74-76, 78-80, 82 and 83 (*Id.*).

As above, the limitations of claims 18 and 28, are not patentable over the cited art because they amounts to a recitation of an infinite range of concentrations, which is not considered inventive. Thus, the limitations of each of dependent claims 11-18, 22-28, 44, 46, 58-64, 67-71, 73, 74-80, 82, 83-85 and 91-93 would have been obvious to the ordinary skilled artisan at the time of filing.

Response to Applicant's Comments on Vacatur and Remand

The combination of Evan and Tari ('978) Patent Clearly Teaches Away

Applicant's point that the statement of Tari *et al.* to combine oligonucleotides and lipids that are "compatible" teaches away from the combination of the oligonucleotide of Evan *et al.* with a neutral phospholipid is found persuasive. However, this teaching actually supports combination of the neutral oligonucleotide of Tormo *et al.* and Reed with the neutral phospholipid of Tari *et al.* Therefore, the argument is not persuasive with regard to the present rejections.

The '911 Patent is not Relevant and Not Prior Art

Applicant's assertion that the '911 patent is not available as prior art under any section of 102 is in error. The patent does, in fact, qualify under 35 U.S.C. §102(e). However, upon filing of the CPA, the '911 patent was disqualified as prior art under 35 U.S.C. §103 due to the 35 U.S.C. §103(c) exception for commonly owned patents.

The Rule 132 Declaration

Applicant asserts that the Board seems to recognize that the difference shown in the Rule 132 declaration may be sufficient rebuttal of a prima facie obviousness rejection if Evan is the base reference.

However, it should be noted that the Board also states, "in considering evidence of unexpected results, it has been held that 'the basic property of utility must be disclosed in order for affidavit evidence of unexpected properties to be offered.' *In re Davies*, 475 F.2d 667, 670, 17 USPQ 381, 385 (CCPA 1973). It does not appear that the specification of this application

describes the unexpected results which are now urged" (page 16, second paragraph). Upon careful review of the application, the examiner can find no description of the favorable properties disclosed in the Rule 132 declaration. Therefore, even if the declaration were sufficient to demonstrate unexpected results, the specification fails to disclose the basic property of utility.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DMS

DAVID GUZO
PRIMARY EXAMINER